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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,594	11/14/2003	Mohamed Attawia	3518.1012-005	3230

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EXAMINER	
STANDLEY, STEVEN H	
ART UNIT	PAPER NUMBER
1649	

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12/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,594	ATTAWIA ET AL.	
	Examiner	Art Unit	
	Steven H. Standley	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,11-17,20-24 and 31-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 11-17, 20-24, 31-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

RCE

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/05/2006 has been entered.

2. Claims 1-7, 11-17, 20-24, and 31-34 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

IDS

3. Applicant's IDS submitted 11/05/07 has been considered.

Rejections/Objections: Maintained or New

Priority

4. The examiner maintains that the instant application was only enabled as of the application 10/714,559 filing date, 11/13/03, for the reasons made of record in the prior 3 actions of 9/10/07, 3/12/07, and 9/07/06. Applicant argues again that prophetic examples can be used to provide support. As argued previously, the prior applications disclose administration of a composition comprising firstly a cytokine antagonist, and secondly a laundry list of other generic hormones, glycoproteins, carbohydrates and in

some embodiments mesenchymal stem cells. The applications prior to 10/714,559 did not contemplate the instant invention administered singularly as is claimed.. The invention disclosed is the administration of a generic cytokine antagonist in a composition with mesenchymal stem cells or a laundry list of other things in the prior applications. Therefor, Applicants arguments are not found persuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-3, 5-16, 20-26, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakai et al (Biomaterials, September, 2003; disclosed in applicant's IDS).

Rejection of claims 1-3, 6, 11-16, 20-24, 31, and 33 under 35 USC § 103(a) is maintained for the reasons made of record in the office action dated 9/17/06, 3/12/07, and 9/10/07. Applicant's arguments have been fully considered and not found to be persuasive. Applicant argues first that Sakai et al does not teach or suggest Applicant's claimed invention because Sakai cultures the mesenchymal stem cells. This is not found persuasive because, as made clear previously, Sakai et al. practices a more difficult method for the purposes of labeling the cells to confirm that they had survived in

vivo. Applicant then argues to conflicting points on pages 7 and 8 of Remarks dated 11/05/07. Applicant argues on page 7 that, "It was standard practice in the art to culture clinically useful cells. The references discussed in the previous amendment were published at or before the time of the invention and all teach culturing clinically useful cells outside of the context of marking, and demonstrate that one of ordinary skill in the art at the time of the invention would have been motivated to culture cells prior to administration." This is simply not true. One of ordinary skill in the art would know that autologous cell administration has been a standard practice for bone-marrow transplants, blood transfusions, skin, and hair grafts long before the relevant priority date of 11/13/03.

Applicant argues on page 8 that, "Sakai's culturing of stem cells would not be desirable for treatment of degenerative disc disease because culturing results in a large stem cell population. It is not desirable to have a large stem cell population because one would not want to overburden the bodily system with nutritional requirements for feeding large numbers of such cells. In addition, the degenerative disc can only hold a limited number of cells." This is not found persuasive because Sakai et al does not administer all of the cultured cells. In fact, Sakai et al. administer 0.04 ml of cells at $1x10^6$ cells/ml (page 3533, Sakai et al.). That's 40,000 cells per animal. In other words, Sakai et al. are injecting a very small amount of cells probably comparable (absent evidence to the contrary) to the amount that would have been injected had Sakai et al skipped the culture step. Applicant also says that one of skill in the art would have been motivated to culture (and expand) the cells prior to administration. This is clearly not Sakai et al.'s

motivation because they don't administer a lot of cells. They administer a very small amount. Therefor Sakai et al provide one of ordinary skill in the art with motivation to use only a small amount of cells that would be comparable to that obtained by using isolated autologous cells immediately. Sakai et al culture the mesenchymal stem cells so that they can introduce a marker to verify cells have survived. Without the burden to demonstrate that the applied cells were alive and integrated, Sakai et al would not have had to culture the cells.

Applicant argues on page 8 of Remarks that it is a serious disadvantage to culturing because it takes weeks. The examiner agrees and further assets (as he has in prior actions) that the motivation to administer uncultured cells is that the procedure can be performed in hours instead of days. However, the examiner also points out that this is not a limitation

Applicant argues on page 9 that the invention satisfied a long-felt need. This is not found persuasive because Applicant has provided no objective evidence of such. There is not statement or evidence in the art of record that establishes that autologous administration of uncultured stem cells was a long-felt need.

Regarding amendments to claims 15, and 33, Sakai et al. does not teach administering in a volume of 0.5 to 3 ml to an intervertebral disc. This is because Sakai et al administers to rats in a model of disc injury. Sakai et al. administers 0.04 ml into the nucleus pulposus of the rat because rats obviously have smaller vertebrae and discs. One of ordinary skill would chose to administer a volume appropriate for

humans. In other words, it would be a matter of routine optimization to adapt the method of Sakai et al to humans with appropriate volumes.

6. Claims 1-3, 6, 10-16, 31, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakai et al. as applied to claims 1-3, 6-16, 20-26, and 31, and further in view of El-Khoury et al (1991).

Sakai et al transplant cultured autologous mesenchymal stem cells embedded in a hydrogel 'carrier' (Atelocollagen) into intervertebral discs of L2-L3, L3-L4, L4-L5 through a 27-Gauge needle (which is smaller than 24 gauge,' see page 3533, Sakai et al), meeting the limitations of claims 1-3, 6, 10-11, 16, 23-24. Stem cells were concentrated by centrifugation before administration (see page 3532, Sakai et al). Sakai et al embed the cells in Atelocollagen gel with low-glucose, which is a nutritional supplement, meeting the limitations of claims 7-8, 12 (see 3533, left col). White rabbits were fed during the experiment, meeting the limitations of claim 13. White rabbits were fed after being treated with mesenchymal stem cells, meeting the limitations of claim 14. Sakai et al report a volume administered to white rabbits of 8 ml (see page 3533), meeting the limitations of claim 15. Sakai et al administer into the intervertebral disc with a 27-Gauge needle which deposits, absent evidence to the contrary, embedded cells into and around the annulus fibrosus and the nucleus pulposus, meeting the limitations of claims 20-21. Sakai et al remove a portion of the nucleus pulposus (page 3533, right col, section 2.5), thereby meeting the limitations of claim 22. The cells of Sakai et al are comprised of all the type cited in claim 25, and

Sakai refers to the stem cell mix as 'mesenchymal,' meeting the limitations of claim 26. Sakai et al. teach administration to each animal in the volume of 0.04 ml, meeting the limitations of claim 31 (see page 3533, section 2.6).

Sakai does not teach injecting the autologous mesenchymal stem cells without culture. However, it would be obvious to do so, since the role of culturing is simply to add a marker to the cells so that the cells can be distinguished from cells that have not been isolated.

It would be obvious to one of ordinary skill in the art to isolate the instant cells from a patient and add them *directly* to the interverterbral disc without culturing because cultured cells work and one would be motivated to do so because it would take hours instead of weeks to perform the transplantation.

There would be a reasonable expectation of success because cells that are culture for weeks, such as in Sakai et al., are still viable and therapeutic. Therefore newly isolated cells would be expected to work just as well, if not better. In summary, the instant claims are to a method of Sakai et al without culturing. However, Sakai et al. does not teach that culturing is necessary, and Sakai et al does not teach away from using the cells directly. Sakai simply cultures the cells so that a beta-galactosidase marker can be added to judge the efficacy and survivability of the transplanted cells. Therefore, Sakai et al instructs one of ordinary skill in the art how to perform the instantly claimed transplantation.

Sakai et al. do not teach administering in a volume of 0.5 to 3 ml to an intervertebral disc.

Notwithstanding routine optimization, El-Khoury et al. administer to an intervertebral disc a total volume of 2.5 ml for the treatment of back pain (see page 688, also see figure 3, left column, El-Khoury et al). Thus, it would be obvious to one of ordinary skill in the art that a similar volume could be used to administer cells to an intervertebral disc. The expectation of success is high because the volume is show to be appropriate for injection to the same area the claims recite.

One would be motivated to combine the teachings of Sakai et al. with El-Khoury et al because Sakai et al. discloses the method in rats, whereas EL-Khoury discloses the injection into the intervertebral disc in humans. EL-Khoury et al. provide an appropriate volume to administer to humans.

7. Claims 1-3, 6, 10-14, 16, 31, and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakai et al. as applied to claims 1-3, 6-16, 20-26, and 31 and further in view of McMillan et al (2002).

Sakai et al teach as described above.

Sakai et al do not teach administration of cells intraoperatively to a patient following harvest from the patient.

McMillan et al teach Intraoperative autologous cell administration wherein the cells are administered to a patient after harvesting from said patient. On page 74, left

column of McMillan et al, they disclose intraoperative red cell salvage and retransfusion of washed (treated) cells. Shed blood is vacuum aspirated and immediately treated with heparin. The cells are essentially separated by centrifugation, washed, and readministered to the patient.

It would be obvious to one of ordinary skill in the art to combine the mesenchymal stem cell treatment of Sakai et al with the intraoperative procedure of McMillan et al because one could treat degenerative discs immediately and without the problem of rejection.

The expectation of success is high because the much more difficult procedure of Sakai et al, wherein the cells were cultured and then readministered, was quite successful.

8. Rejection of claims 1-4, 6, 11-16, 20-24, 31 and 33 under 35 U.S.C. 103(a) as being unpatentable over Sakai et al as applied to claims 1-3, 6-16, 20-26, and 31 above, and further in view of Tanney et al (1980) is maintained.

Applicant argues Sakai et al do not teach their method as therapeutically useful. This is not found persuasive because Sakai et al argues that the transplantation was effective in decelerating disc degeneration (see abstract).

Applicant argues that Sakai et al does not teach the method in particular in using the volumes recited. This is not found persuasive because, as the examiner has

already argued, finding the right volume for administration to humans is a matter of routine optimization.

9. Claims 1-3, 5-7,10-16, 18, 20-24, and 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakai et al as applied to claims 1-3, 6, 11-16, 20-24, 31, and 33 above, and further in view of Russell et al (may 2003 meeting abstract, in applicant's IDS),

Applicant argues on page 12 that the references do not teach administration of cells in the volumes recited (in claims 15, 31, and 33). This is not found persuasive because, as the examiner has already argued, finding the right volume for administration to humans is a matter of routine optimization.

10. Claims 1-3, 6, 10-16, 31, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakai et al. as applied to claims 1-3, 6, 11-16, 20-24, 31, and 33 above, in further in view of Russell et al (2003 meeting abstract, in applicant's IDS), and in further view of El-Khoury et al (1991).

Sakai et al. teaches as described above. Sakai et al. does not teach using TGF-beta in addition to mesenchymal stem cells.

Russell et al teach that bone marrow mesenchymal stem cells can be used as a source for treatment of disc degeneration as Sakai et al does. In

addition, Russell et al teach using TGF-beta to stimulate chondrocyte differentiation (see results and discussion).

Sakai et al. and Russell et al. do not teach administering in a volume of 0.5 to 3 ml to an intervertebral disc.

El-Khoury et al. administer to an intervertebral disc a total volume of 2.5 ml for the treatment of back pain (see page 688, also see figure 3, left column, El-Khoury et al). Thus, it would be obvious to one of ordinary skill in the art that a similar volume could be used to administer cells to an intervertebral disc. The expectation of success is high because the volume is show to be appropriate for injection to the same area the claims recite.

One of ordinary skill in the art would be motivated to combine the references because tgf-beta stimulated mesenchymal cells were stimulated to differentiate into chondrocytic phenotype is critical to mimic disc like-cells. Further, Il-Khoury et al. teaches the appropriate volume to administer in. One would be motivated to use a volume that was appropriate for intervertebral injection.

The expectation of success would be high because all of the elements have been performed, and in fact been performed in the more difficult transplantation process of Sakai et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven Standley whose telephone number is **(571) 272-3432**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Stucker can be reached on **(571) 272-0911**.

The fax number for the organization where this application or proceeding is assigned is **(571) 273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

Steve Standley, Ph.D.
12/10/07

/David Romeo/
Primary Examiner, Art Unit 1647